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# Right Heart Adaptation to Left Ventricular STEMI in Rats

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## Abstract

Development of right ventricular (RV) failure in patients after ST-segment elevation myocardial infarction (STEMI) is common. However, a systematic analysis of chamber-specific changes in the expression of genes linked to cardiac function, apoptosis, fibrosis, receptor responsiveness, and inflammation is lacking. Postischemic remodeling was analyzed in rats that received STEMI in the closed chest mode. Rats were sacrificed at day 1, 3, 7, and 120 after surgery. The mRNA expression of genes was quantified by a real-time RT-PCR. Echocardiography was performed after 120 days. Organ weights and systemic blood pressure were determined in addition. Rats developed left and RV dysfunction within 7 days after ischemia/reperfusion and this lasted until the end of the experiments. However, adaptation to ischemia/reperfusion differed significantly between both ventricles. In the LV, a high expression of MMP12, a neutrophil-specific elastase, indicated a significant inflammatory responsiveness that did not occur in RV. A number of differentially regulated genes in the RV exceeded that of the LV at day 3. Postinfarction RV failure is common in rats with ischemia/reperfusion of the left arterial descending aorta. It is associated with severe RV remodeling that occurred delayed to that of the LV. Changes in RV are independent of the initial inflammation.

**Keywords:** myocardial infarction, cardiac remodeling, right heart failure, inflammation, reperfusion injury

## 1. Introduction

Right ventricular (RV) failure is common in patients with acute ST-segment elevated myocardial infarction (STEMI) and animal models of remodeling post-myocardial infarction [1–3]. The underlying reason for biventricular failure due to myocardial infarction and/or transient ischemic events is not clear but may be a consequence of hemodynamic changes during infarction and ischemic events in the RV as well. Nevertheless, RV failure is a severe complication during the subsequent postinfarct period and a limitation of further prognosis [4]. Therefore, it is important to understand the molecular adaptation of the RV in response to LV infarction.

Molecular and cellular mechanisms involved in cardiac remodeling after myocardial infarction are triggered by transcriptional regulation of genes linked to apoptosis, fibrosis, inflammation, calcium handling, and receptor responsiveness. Some of these adaptive mechanisms occur early after reperfusion and activation of the transcription factor AP-1 have been identified as main factors [5]. However, steady-state mRNA levels depend also from RNA degradation leading to a decrease in the expression of some genes. Thus, steady-state mRNA expression of genes

involved in cardiac remodeling can be increased or decreased. Real-time RT-PCR allows quantification of such molecular and cellular adaptation in tissues and can be used to characterize such changes in a time- and organ-specific manner. This study was aimed to identify differentially regulated cardiac genes in the LV and RV that are involved in cardiac remodeling during postmyocardial infarction.

The left anterior descending coronary artery was occluded in rats for 45 min and subsequently reopened. Success of occlusion and reperfusion was monitored by ECG recordings. Rats were sacrificed after 1, 3, 7, and 120 days and the left and right ventricles were removed and analyzed thereafter. The hemodynamic consequences were recorded by echocardiography.

## 2. Material and methods

### 2.1 Animal models and animal handling

The investigation conforms to the directive 2010/63/EU of the European Parliament. Use of animals was registered at the Justus-Liebig-University (registration-no.: 417-M). The experimental protocols were approved by the ethics committee for animal experimentation of the local authorities in Giessen, Germany and Szeged, Hungary.

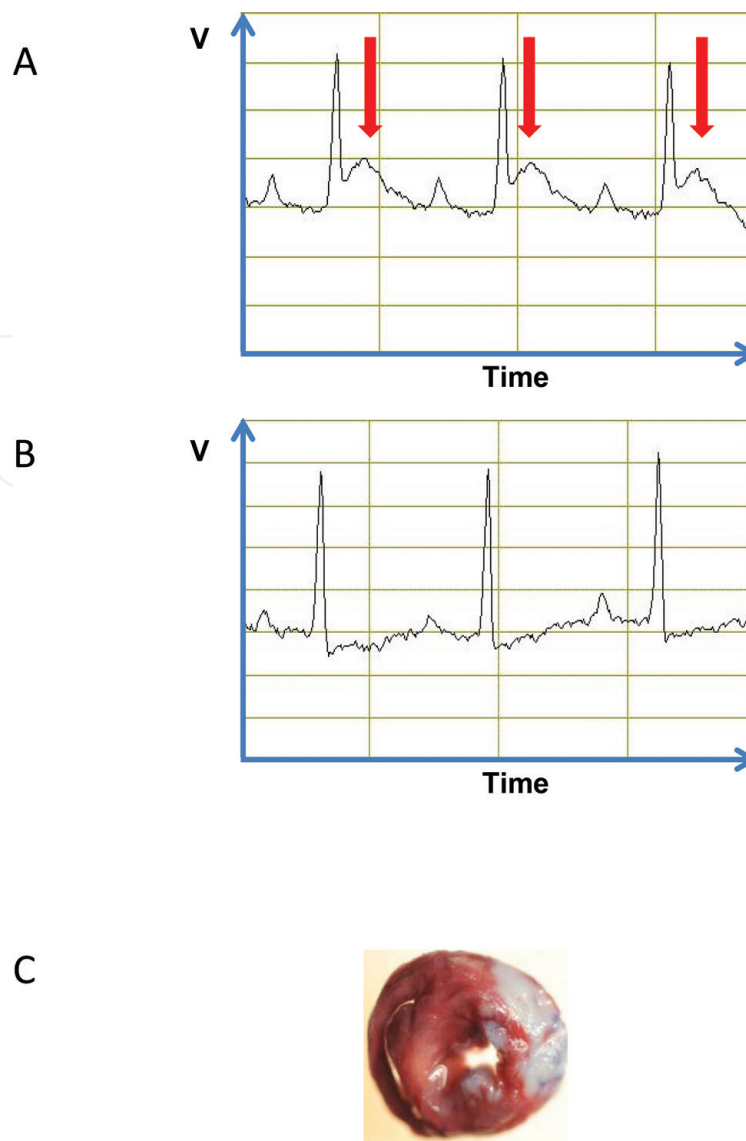
Myocardial infarction and reperfusion was performed in the closed-chest model. To achieve this, rats were anesthetized by inhalation of isoflurane (induction: 5%, maintenance: 2–3%), intubated, and placed on a respirator during surgery to maintain ventilation. Before surgery, 0.03 mg/kg nalbuphine (Nalbuphin Orpha, AOP Orpha Pharmaceuticals, Vienna, Austria) was injected (i.p.). The adequacy of anesthesia was monitored by electrocardiography and pulse rate. A suture was placed around the left anterior descending coronary artery (LAD) and remained subcutaneously [6]. Two hours after the wound closing, 0.03 mg/kg nalbuphine was repeated to alleviate postoperative pain. Seven days later, rats were anesthetized as before and the suture was mobilized and the LAD was occluded for 30 min. The occlusion was monitored by electrocardiography (ST elevation; see **Figure 1**). Thereafter, the occluder was opened again and the suture was cut and the skin was closed in one layer. Sham rats received the same protocol but the occluder was not mobilized after 7 days. Please note that this study is a second end-point analysis of tissue material also used before to characterize the role of arginase in ischemia/reperfusion injury [7].

### 2.2 *Ex vivo* analysis of cardiac function

In order to analyze the cardiac function *ex vivo*, rats were anesthetized again by isoflurane and killed by cervical dislocation. Thereafter, hearts were rapidly excised and the aorta was cannulated for retrograde perfusion with a 16-gauge needle connected to a Langendorff perfusion system. Left ventricular function was determined by insertion of a water-filled balloon into the left ventricle as described before [8]. Hearts were paced during measurements.

### 2.3 *In vivo* analysis of cardiac function

Transthoracic echocardiography was performed as described previously [9] under isoflurane anesthesia (1.5%) at 120 days after ischemia/reperfusion. Briefly, two-dimensional and M-mode echocardiographic examinations were performed in accordance with the criteria of the American Society of Echocardiography with



**Figure 1.**  
 ECG recording during ischemia (A) and after reperfusion (B) indicating ST elevation in these rats (red arrow). (C) TTC staining visualizing the location of the infarct.

a Vivid 7 dimension ultrasound system (General Electric Medical Systems) using a phased array 5.5–12 MHz transducer (10S probe). Data of three consecutive heart cycles were analyzed (EchoPac Dimension software; General Electric Medical Systems) by an experienced investigator in a blinded manner. The mean values of three measurements were calculated and used for statistical evaluation. Functional parameters including left ventricular ejection fraction (EF) and fractional shortening (FS) were calculated on four-chamber view images.

## 2.4 qRT-PCR

After removing the hearts from the Langendorff apparatus, the ventricular tissue was carefully isolated and quickly frozen into fluid nitrogen. Tissue samples were prepared to analyze the steady-state mRNA levels of proteins of interest according to the previously described method [8]. Briefly, total RNA was isolated from the ventricles using peqGoldTriFast (peqlab, Biotechnology GmbH, Germany) according to the manufacturer's protocol. To remove genomic DNA contamination, isolated RNA samples were treated with 1 U DNase per mg RNA (Invitrogen, Karlsruhe, Germany) for 15 min at 37°C. One microgram of total RNA was used in 10 µl reaction to synthesize cDNA using superscript RNaseH

	Forward	Reverse
ANP	ATG GGC TCC TTC TCC ATC AC	TCT TCG GTA CCG GAA GCT
BNP	ATG ATT CTG CTC CTG CTT TTC	TCT GCA TCG TGG ATT GTT CTG
MHC- $\alpha$	CAC CCT GGA GGA CCA GAT TA	TGG ATC CTG ATG AAC TTC CC
TGF- $\beta_1$	ATT CCT GGC GTT ACC TTG G	CCT GTA TTC CGT CTC CTT GG
Biglycan	TGA TTG AGA ATG GGA GCC TGA G	CCT TGG TGA TGT TGT TGG AGT G
Decorin	GGC AGT CTG GCT AAT GTT C	CTT CGG AGA TGT TGT TGT TAT G
Collagen-1	GCG AAC AAG GTG ACA GAG	CCA GGA GAA CCA GCA GAG
Collagen-3	TGG AGT CGG AGG AAT G	GCC AGA TGG ACC AAT AG
Elastin	TGC TAC TGC TTG GTG GAG AAT G	CGT GGC TGC TGC TGT CTG
Fibronectin	TGG AGC AAG AAG GAC AAC	CGG ACA TCT GTG AAG GAG
Laminin	CGA GGA TGT CAG CGT TGT	TCA CAG CCG TCT CCA GTC
SERCA2a	CGA GTT GAA CCT TCC CAC AA	AGG AGA TGA GGT AGC GGA TGA A
Phospholamban	TAT GTC TGC TGC TGA TAT GC	ACT CTT AAA TCG TGA CCC TTC
NCX	CGC TAA TCA GCA TTT CAG AG	GCC AGG TTC GTC TTC TTA AT
Bax	ACT AAA GTG CCC GAG CTG ATC CAC	TGT CTG CCA TGT GGG G
Bcl-2	ATC TTC TCC TTC CAG CCT GA	TCA GTC ATC CAC AGA GCG AT
ODC	GAA GAT GAG TCA AAC GAG CA	AGT AGA TGT TTG GCC TCT GG
Arginase-2	TGA GGA GCA GCG TCT CCC GT	GCT TCT CGG ATG GCG GCT GG
eNOS	AGC CCG GGA CTT CAT CAA TCA G	GCC CCA AAC ACC AGC TCA CTC TC
Intermedin	TGC CTC AGG GTG GTG GCT CAA CT	GTG GGG GCT GCT GGG AT
RAMP-1	AGC ATC CTC TGC CCT TTC ATT	GAC CAC CAG GGC AGT CAT G
RAMP-2	GCA GCC TAC CTT CTC CGA TCC	TCC TCC ACA CCA CAA GCG TAA C
RAMP-3	CAA CCT GTC GGA GTT CAT CGT	TGT CTC CAT CTC CGT GCA GTT
MMP9	CAA TCC TTG CAA TGT GGA TG	AAA TCT TCT TGG ACT GCG GA
MMP12	TGC AGC TGT CTT TGA TCC AC	GCA TCA ATT TTT GGC CTG AT
iNOS	AAG AGA CGC ACA GGC AGA G	CAG CAG GCA CAC GCA ATG
Nrf-1	GGC ATC ACT GGC AGA GGC CG	GCT GCT GCG GTT TCC CCA GA
PGC-1 $\alpha$	AGT GCT CAG CCG AGG ACA CGA	TGC CCC TGC CAG TCA CAG GA
SDF-1 $\alpha$	CCA AGG TCG TCG CCG TGC TG	GGC TCT GGC GAC ATG GCT CT
VEGF	TGC CCC TAA TGC GGT GTG CG	GGC TCA CAG TGA ACG CTC CAG G
GATA4	CTA TGG CCG CCA ACC ACG GG	CGC GGA GTG GGC ACG TAG AC
Mef-2c	CAG TTG GGA GAC CGT ACC AC	GTG AGT CCA ATG GGG GAG TG
Nkx.2a	CAC ACG CCC TCC TCA GTC AA	GAG TAG CCG TCC GGC TTG AA
vWF	AAG ATG GCA AGA GAG TGG GC	CCG TAG GCC TCA CTG GAA AG
VE-cadherin	CCA GAA TTT GCC CAG CCC TA	GTC CTC GTT CTT CAG GGC AA
B2M	GCC GTC GTG CTT GCC ATT C	CTG AGG TGG GTG GAA CTG AGA C
HPRT	CCA GCG TCG TGA TTA GTG AT	CAA GTC TTT CAG TCC TGT CC

**Table 1.**  
*List of primers used in this study.*



reverse transcriptase (200 U/ $\mu$ g; Invitrogen) and oligo dTs (Roche, Mannheim, Germany) as primers. Reverse transcriptase reactions were performed for 60 min at 37°C. Real-time PCR was performed using the Iqycler IQ detection system (Bio-Rad, Munich, Germany) in combination with IQ SYBR Green real-time supermix (Bio-Rad). A complete list of all primers used in this study is given in **Table 1**. Data are normalized to hypoxanthine phosphoribosyltransferase (HPRT) expression that was used as a house-keeping gene in this study. Preliminary experiments with  $\beta$ 2 microglobulin, which was alternatively considered as house-keeping gene, revealed similar results but higher variability. The relative change in expression was quantified by the  $\Delta\Delta C$  method [10].

## 2.5 Statistics

The results are expressed as means  $\pm$  S.E.M or median with 25 and 75% quartiles as indicated in the legend to the figures. Statistical comparisons were performed by two-side T-Test or Mann-Whitney Test. Levene test was used to check the normal distribution of the samples. A p value of 0.05 was considered as statistical significant.

## 3. Results

### 3.1 Weight of organs, left ventricular pressures, and biventricular functions analysis over time

Body weight, LV weight, RV weight, lung wet weight, and kidney weight increased during the 4-months observation period in sham rats and those undergoing ischemia/reperfusion (**Table 2**). Mean increase in body weight at day 3 after the ischemic event was smaller in the surgery group (+2 g) versus the sham group (+13 g) indicating a small impact of the surgery on general behavior. Differences between both groups in ventricular weight occurred only for the RV at day 1 (**Table 1**). RV weights of rats in the experimental group normalized thereafter. No differences were obtained for lung and kidney weights (**Table 2**). Necrotic tissue was nearly exclusively seen in LV (**Figure 1**).

LV function was determined in vitro. Immediately after ischemia/reperfusion, a significant decline in cardiac function was observed but this was normalized thereafter (**Table 3**). Biventricular function was analyzed after 120 days via echocardiography. RV fractional area change (four-chamber view) and LV ejection fraction (longitudinal four-chamber view) were significantly lower in rats of the experimental group compared to shams (**Table 4**).

### 3.2 Biventricular gene regulation over time

In total, biventricular expression of 36 genes was analyzed by a real-time RT-PCR. These genes cover the following area of interest: cardiac hypertrophy (ANP, BNP, MHC- $\alpha$ ), fibrosis (TGF- $\beta$ <sub>1</sub>, biglycan, decorin, collagen-1, collagen-3, elastin, fibronectin, laminin, MMP9), intracellular calcium handling (SERCA2a, phospholamban, NCX), apoptosis (bax, bcl-2), arginine metabolism (ODC, arginase-2, eNOS), receptor coupling (intermedin, RAMP-1, -2, -3), inflammation (iNOS, MMP12), cardiac metabolism (Nrf-1, PGC-1 $\alpha$ ), stem cell mobilization (SDF-1 $\alpha$ , CXCR4, VEGF), cardiac transcription factors (GATA-4, Mef-2c, Nkx.2a), and endothelial markers (von Willebrand factor (vWF), VE-cadherin). **Figure 2** shows how many of these 36 genes were either

	BW	LV/BW	RV/BW	Lung/BW	Kidney/BW
	(g)	(mg/g)	(mg/g)	(mg/g)	(mg/g)
Day 1					
Sham	208 ± 28	2.76 ± 0.37	0.48 ± 0.10	8.38 ± 2.06	5.87 ± 0.65
I/R	209 ± 16	2.87 ± 0.16	0.66 ± 0.07	8.90 ± 3.01	6.94 ± 2.11
P value	0.958	0.317	0.003	0.711	0.222
Day 3					
Sham	222 ± 17	2.64 ± 0.11	0.57 ± 0.06	8.14 ± 2.00	6.05 ± 0.39
I/R	211 ± 21	2.69 ± 0.22	0.64 ± 0.10	7.28 ± 0.77	5.77 ± 0.25
P value	0.292	0.550	0.135	0.674	0.133
Day 7					
Sham	222 ± 20	2.69 ± 0.15	0.51 ± 0.08	7.47 ± 0.95	5.80 ± 0.36
I/R	225 ± 22	2.93 ± 0.25	0.51 ± 0.07	7.81 ± 1.43	6.03 ± 0.61
P value	0.775	0.054	1.000	0.613	0.389
Day 120					
Sham	255 ± 16	2.69 ± 0.13	0.53 ± 0.06	8.84 ± 1.81	5.85 ± 0.34
I/R	256 ± 21	2.74 ± 0.52	0.55 ± 0.12	9.89 ± 1.08	6.32 ± 0.73
P value	0.908	0.736	0.666	0.211	0.210
Data are means ± S.D. from n = 8–9 rats. Data are given for body weight (BW), left ventricular weight (LV), right ventricular weight (RV), lung weight, and kidney weight. Data for LV, RV, lung, and kidney were normalized to body weight.					

**Table 2.**  
Body weight and organ weight.

	Sham	I/R	Δ	P value
Day 1	157.5 ± 20.9 mmHg	122.9 ± 21.7 mmHg	Δ = −34.6 mmHg	0.006
Day 3	155.0 ± 23.8 mmHg	132.0 ± 30.1 mmHg	Δ = −23.0 mmHg	0.113
Day 7	188.2 ± 31.4 mmHg	162.1 ± 15.4 mmHg	Δ = −26.1 mmHg	0.054
Day 120	144.4 ± 10.4 mmHg	137.9 ± 22.3 mmHg	Δ = −6.5 mmHg	0.442
Data are means ± S.D. from n = 8–9 hearts.				

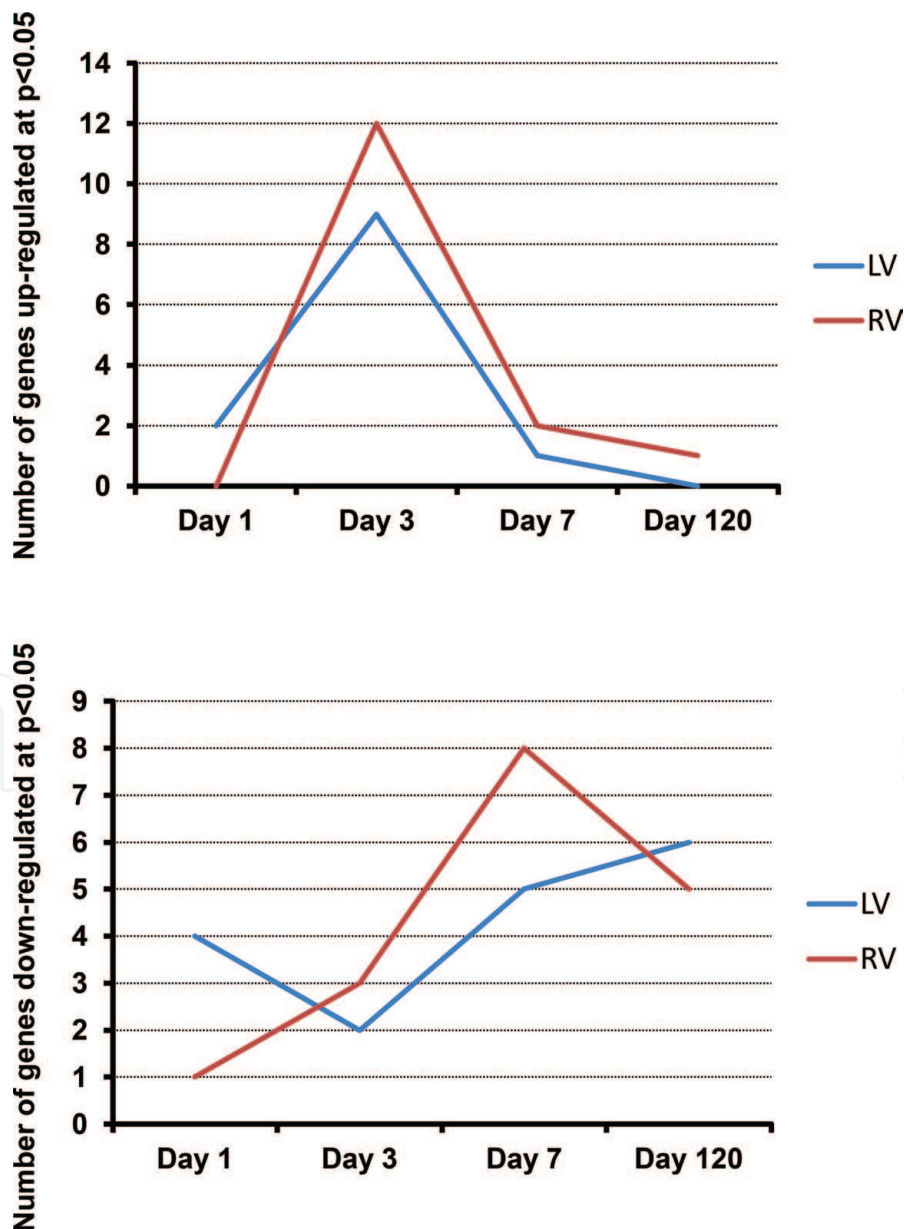
**Table 3.**  
Left ventricular developed pressure (LVDP).

	Sham	I/R	Δ	P value
LV EF	65.0 ± 5.8	51.3 ± 8.1	Δ = −13.7%	0.000
RV FAC	55.8 ± 7.2	45.5 ± 7.2	Δ = −10.3%	0.004
Data are means ± S.D. from n = 9–13 rats. LV EF = left ventricular ejection fraction (determined by four-chamber longitudinal view); RV FAC = right ventricular fractional area change (determined by four-chamber view).				

**Table 4.**  
Biventricular function determined by echocardiography.

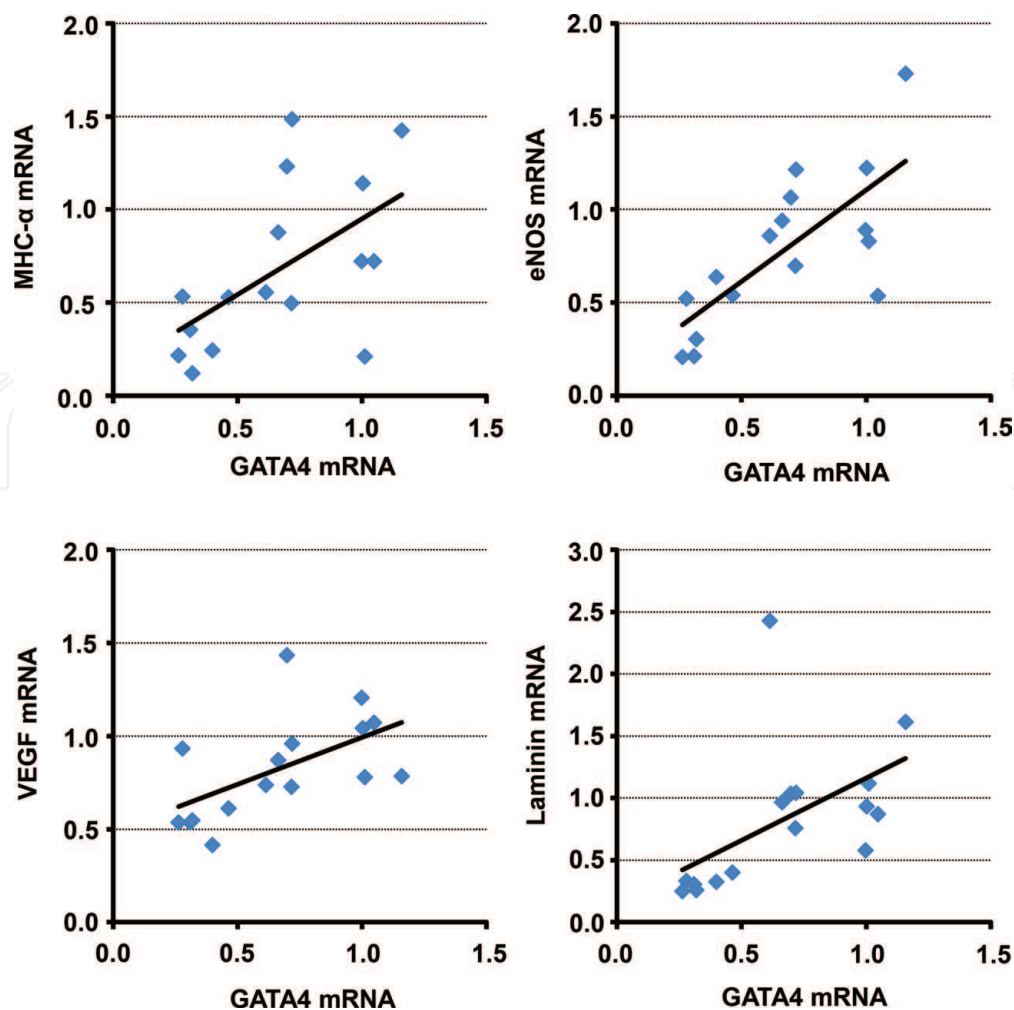
upregulated or downregulated in the two ventricles over the time. In general, there was an upregulation of several genes mainly at day 3 postinfarction, whereas a downregulation of genes dominated at days 7 and 120. At the first time point (day 1),

there were significant differences in the expression between both ventricles. In the LV, four genes were significantly downregulated: GATA4, VEGF, eNOS, and MHC- $\alpha$ . VEGF, eNOS, and MHC- $\alpha$  genes contain a GATA4 promoter region. As expected, GATA4 expression correlated significantly with that of VEGF, eNOS, and MHC- $\alpha$  (**Figure 3**). Only two genes were upregulated (MMP12, Mef2c) at that time point. As MMP12 is a neutrophil-specific elastase, its strong expression in LV may indicate leukocyte infiltration into the LV during initial tissue repair. In the RV, only one gene was significantly affected by myocardial ischemia/reperfusion at that time (NCX). **Figure 4** shows the relative expression of all genes including those that were either up- or downregulated but without reaching the level of significance. At day 1, there is more variability and, therefore, more transcriptional adaptation in LV compared to RV. In the LV, the strongest downregulation that was not yet significant ( $>0.05$ ) was found for laminin (again correlated with GATA4; **Figure 3**). The strongest upregulation that was not yet significant was found for MMP9. However, lack of statistical significance for laminin and MMP9 indicates a high interindividual variability. In the RV, ANP and Nkx.2a were strongly upregulated and collagen-3 was strongly downregulated but yet not significant.



**Figure 2.**  
*Time-dependent induction gene regulation in both ventricles. Note that the number of genes differentially regulated (cutoff  $p < 0.05$ ) is increased in RV after 3 days.*

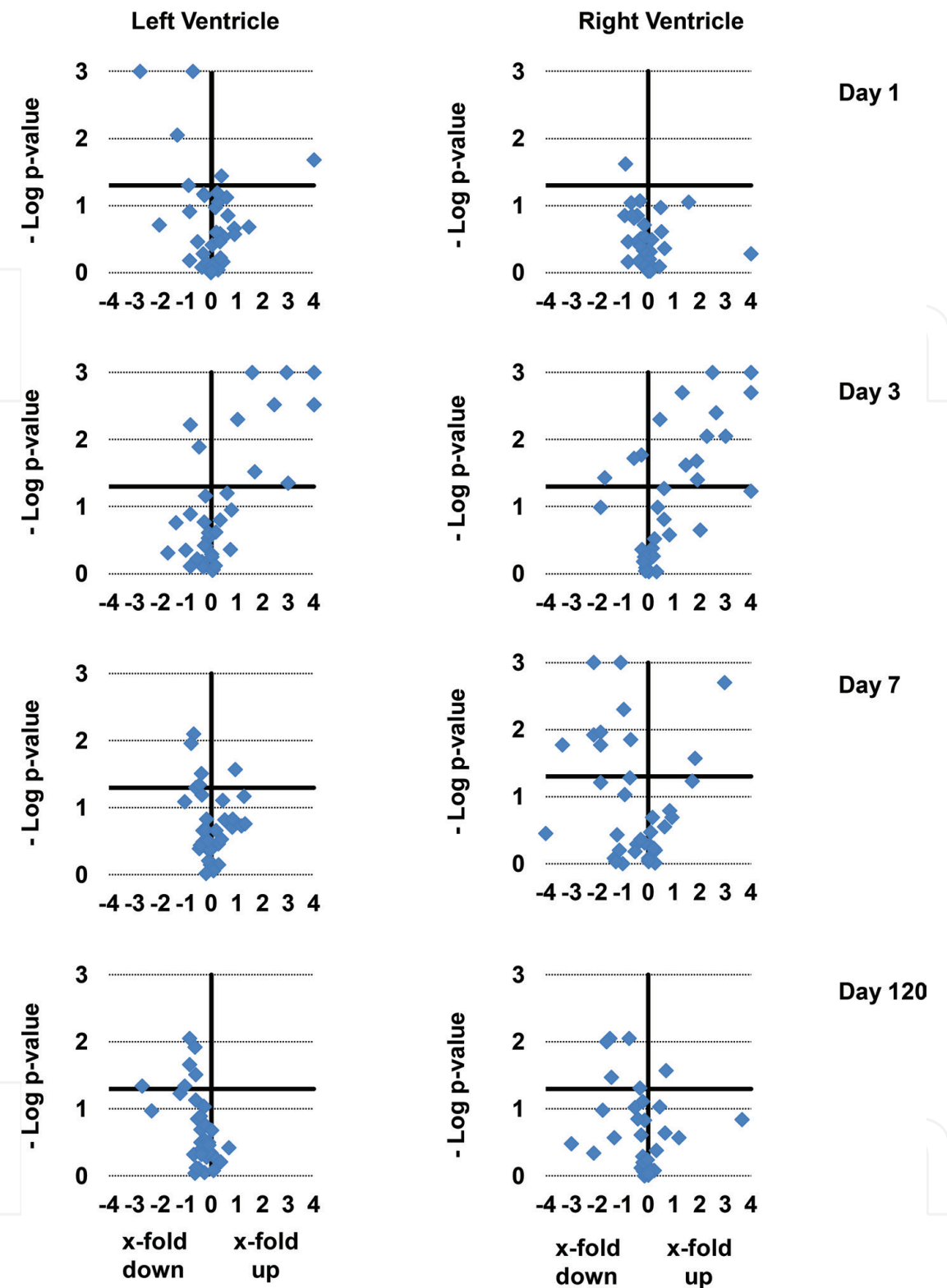




**Figure 3.**  
Correlation between *GATA4* expression and that of *GATA4*-dependent regulated genes.

At day 3, there were many genes significantly upregulated in both ventricles such as BNP, MHC- $\alpha$ , SERCA2a, phospholamban, NCX, and VEGF. ANP and PGC-1 $\alpha$  were also significantly upregulated but in both ventricles. However, the individual variability in RV was strong for these genes so that the level of induction did not reach the level of significance. An exception from the coregulation of genes between both ventricles is the transcription factor Nkx2a. Nkx2a was upregulated in the LV but beyond the level of detection in the RV. At day 3, only two genes were downregulated in the LV. These are RAMP-2, that was similarly downregulated in the RV and vWF that was slightly reduced in the RV. In addition to the aforementioned genes, six genes were specifically upregulated in the RV that were not induced in the LV. These were decorin, collagen-3, eNOS, RAMP-3, MMP12, and Nrf-1. The increased expression of most of these genes is indicated in the plot shown in **Figure 4**.

At day 7, the expression of most genes induced at early time points was normalized again. However, at that time point, many genes were significantly downregulated. In the LV, this holds for NCX, intermedin, PGC-1 $\alpha$ , vWF, and VE-cadherin. Only VE-cadherin and intermedin were also downregulated in the RV; although due to the high individual variability of the RV, this does not reach the level of significance. Only biglycan was induced in the LV at this time point. The gene expression profile of the RV differed significantly from that of the LV at this time point. SERCA2a and NCX were still strongly induced. TGF- $\beta$ 1, bax, bcl-2, RAMP-1, RAMP-2, iNOS, Nrf-1, and CXCR4 were all significantly downregulated. The level of regulation strongly increased the level of regulation of these genes in the left ventricle. **Figure 4** summarizes the expression of all genes at that time point.



**Figure 4.**  
*Profile of gene expression at days 1, 3, 7, and 120 in both ventricles. Upregulated genes are on the right side. Above the horizontal bar differences are below  $p < 0.05$ .*

At day 120, 6 out of 36 genes under investigation were downregulated in the LV. These were decorin, RAMP-1, MMP9, MMP12, GATA4, and vWF. Among them, only GATA4 and vWF were not similarly downregulated in the RV. Elastin, fibronectin, bax, and Nkx.2a were specifically downregulated in the RV. Except for Nkx.2a, similar changes (although not significant) were also seen in the LV. The expression of SERCA2a was induced in the RV at that time but not in the LV. Overall, a stronger transcription adaptation is seen in the RV at that time (Figure 4).

## 4. Discussion

This study investigated transcriptional adaptation in LV and RV following ischemia/reperfusion in vivo up to 120 days. A higher gene expression level has been attributed to better postinfarct adaptation in female versus male mice [11]. Here, differences were found between both ventricles in the very early phase after ischemia/reperfusion. A significant downregulation of the transcription factor GATA-4 was found specifically in the LV 24 h after reperfusion confirming similar findings after 2 h [11]. According to this observation, the expressions of GATA4-dependent genes (MHC- $\alpha$ , eNOS, and VEGF) were also downregulated. GATA-4 can exert cell survival signaling in cardiac myocytes and delivery of GATA-4 locally to the infarct border zone induces multiple local effects resulting in beneficial remodeling [12, 13]. Regardless of these initial differences, similar changes, mainly induction of gene expression, were found in both ventricles after 3 days. In both ventricles, repression of cardiac gene expression was more prominent rather than induction at later time points, specifically after 4 months. At that time point, the expression profile significantly differed between both ventricles with a more adaptive phenotype in the RV. Again, at this later time point, reduced expression of GATA4 seems to account for some of the differentially downregulated genes in the LV. In summary, this study highlights the differential expression of GATA4 in LV and RV after successful reperfusion and correlates the expression of GATA4 with main differences in molecular adaptation between both ventricles. Regardless of the different molecular adaptation, LV and RV developed a drop of function although the infarct area and inflammation was specifically located at the left ventricle.

The cardiac ventricle is able to respond to ischemic stress with changes in steady-state mRNA levels within 24 h. In principle, steady-state levels of mRNA are the sum of mRNA formation and degradation and the quantification of steady-state levels does not necessarily identify mechanisms that cause these changes. However, in the current study, the main changes in ventricular expression that occurred within 24 h in the LV corresponded to genes that are known to obtain a GATA-4 promoter responsive element. Please note that only the LV is exposed to ischemia/reperfusion. Moreover, GATA-4 itself was also downregulated. It should be noted that within the first few hours after the ischemic event, transcriptional changes were mainly present in the LV.

The response of the heart to LV ischemia and reperfusion significantly differed at day 3. At that time, strong molecular adaptations were obtained in both ventricles. In most cases, these were linked to an upregulation of genes indicating an active adaptation to the postischemic stress. Interestingly, most genes that were upregulated in the LV were also regulated in the RV. An exception to this rule was Nkx.2a. This cardiac-specific transcription factor was below the level of detection in the RV but induced in the LV, probably indicating an active regenerative process. This may indicate cardiac differentiation of cells infiltrated into the infarct-affected ventricle (possibly circulating stem cells), or a cardiac differentiation of cells that were located in the LV and that still have a potential to differentiate (cardiac progenitor cells). Alternatively, it may indicate an active repair process of terminally differentiated cardiomyocytes (hypertrophy). However, the more important finding was the observation that a couple of genes were specifically upregulated in the RV that are not induced in the LV. As such decorin, an endogen inhibitor of the profibrotic cytokine TGF- $\beta$ 1, eNOS, increasing the bioavailability of nitric oxide, and Nrf-1, improving mitochondrial biogenesis, were identified. Each of these factors is a marker of compensatory hypertrophy.

One week after the ischemic event, the initial activation of gene transcription is normalized and replaced by downregulation of many genes in LV and

RV. Interestingly among them are endothelial cell markers and genes linked to cardiac metabolism. Thus, the molecular adaptation switches into a profile of maladaptation. In concert with this view, biglycan, a factor that favors fibrosis, was induced in the LV. In the RV, the expression of profibrotic genes was downregulated as well as the expression of inflammatory markers. Again, the molecular adaptation of the RV seems to be more favorable than that of the LV.

Four months after the ischemic event, the cardiac function was reduced in both ventricles. At that time, decorin was downregulated in both ventricles. Moreover, the RV was characterized by downregulation of elastin and fibronectin. Both molecules are required for a proper cardiac function. In summary, although the molecular adaptation of the RV to LV myocardial infarction differs from that of the LV, the corresponding molecular adaptation of the RV leads to dysfunction of the RV as well.

In this study, we analyzed also the expression of intermedin and the receptor activation modifier proteins (RAMP). They have been analyzed with respect to cardiac regulation in the context of pressure-induced hypertrophy but data on the expression in ischemia and reperfusion are lacking. Intermedin (=adrenomedullin-2) potentially stabilized cardiac function by binding to CGRP receptors that are linked to RAMP-1, -2, or -3. This study shows a downregulation of intermedin in the RV at day 3 and in the LV at day 7. Thus, it is differentially regulated during the subsequent molecular adaptation after ischemia/reperfusion but not as a direct response to the ischemic event itself. Significant downregulation of RAMP-2 and RAMP-1 days after myocardial infarction in both ventricles (RAMP-2) and specifically in the RV (RAMP-1) suggests an impairment of receptor signaling during CGRP-receptors during the subsequent remodeling process. As the development of cardiac dysfunction occurred in both ventricles within 4 months, this observation requires future work because this may be a likely candidate for the subsequent development of heart failure.

Finally, it should be mentioned that this study has of course some limitations. Firstly, data are restricted to genes which mRNA steady-state levels are different between sham and ischemia/reperfusion at a p value of 0.05. This does not exclude the possibility that genes that are strongly regulated but below a p value of 0.05 due to a higher individual variation are not relevant for the molecular adaptation. Secondly, the level of significance is a variable of the n number of animals that are investigated. Here, we used eight rats per group. A lower n reduces the number of genes identified as significantly regulated. However, these limitations are counterbalanced by the quantitative real-time RT-PCR protocol and even more important by the high number of genes under investigation and the analysis of groups of genes linked to specific adaptations (i.e., linked to fibrosis, apoptosis, etc.). This allows a more general view on the adaptation process.

In conclusion, the study identifies a time-dependent difference in the response of LV and RV to STEMI. In the early phase of LV remodeling, GATA-4-dependent downregulation was dominant. The novel and important finding from this study is, however, that a delayed but significant molecular adaptation of the RV. This RV adaptation in the absence of necrosis seems to be more adaptive but still not sufficient to preserve the function. The regulation of RAMP-2 in both ventricles may be one candidate for future research.

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